Therapy

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Therapy (in Greek: **θεραπεία**), or **treatment**, is the attempted remediation of a health problem, usually following a diagnosis. In the medical field, it is synonymous with the word "treatment". Among psychologists, the term may refer specifically to psychotherapy or "talk therapy".

Therapy	
Intervention	
MeSH	D013812

Preventive therapy or **prophylactic therapy** is a treatment that is intended to prevent a medical condition from occurring. For example, many vaccines prevent infectious diseases. An **abortive therapy** is a treatment that is intended to stop a medical condition from progressing any further. A medication taken at the earliest signs of a disease, such as at the very symptoms of a migraine headache, is an abortive therapy.

A **supportive therapy** is one that does not treat or improve the underlying condition, but instead increases the patient's comfort.[1] Supportive treatment may be used in palliative care.

Overtreatment is an **overutilization**, a treatment that is unnecessary or disproportionate to the situation. For example, the treatment of a condition that causes no symptoms and will go away on its own is overtreatment. Similarly, extensive treatment for a condition that could be remedied with very limited treatment is overtreatment. Overtreatment may be caused by overdiagnosis, the identification of harmless abnormalities.

Contents

Adverse effects

Main articles: Adverse drug reaction and Adverse effect

In addition to (or in place of) the intended therapeutic effect of a treatment, a therapist may cause undesired (adverse) effects as well. When an adverse effect is weaker than the therapeutic effect, one commonly speaks of a "side effect".

An adverse effect may result from an unsuitable or incorrect dosage or procedure (which could be due to medical error). Some adverse effects occur only when starting, increasing or discontinuing a treatment. Using a drug or other medical intervention which is contraindicated may increase the risk of adverse effects. Patients sometimes quit a therapy because of its adverse effects. The severity of

adverse effects ranges from nausea to death. Common adverse effects include alteration in body weight, change in enzyme levels, loss of function, or pathological change detected at the microscopic, macroscopic or physiological level.

Adverse effects may cause a reversible or irreversible change, including an increase or decrease in the susceptibility of the individual to other chemicals, foods, or procedures (e.g. drug interaction).

Difference between preventions, treatments, and cures

A prevention or preventive measure is a way to avoid an injury, sickness, or disease in the first place, and generally it will not help someone who is already ill (though there are exceptions). For instance, many babies in developed countries are given a polio vaccination soon after they are born, which prevents them from contracting polio. But the vaccination does not work on patients who already have polio. A treatment or cure is applied after a medical problem has already started.

A treatment treats a problem, and may lead to its cure, but treatments often ameliorate a problem only for as long as the treatment is continued, especially in chronic diseases. For example, there is no cure for AIDS, but treatments are available to slow down the harm done by HIV and delay the fatality of the disease. Treatments don't always work. For example, chemotherapy is a treatment for some types of cancer. In some cases, chemotherapy may cause a cure, but not in all cases for all cancers. When nothing can be done to stop or improve a medical condition, beyond efforts to make the patient more comfortable, the condition is said to be **untreatable**. Some untreatable conditions naturally resolve on their own; others do not.

Cures are a subset of treatments that reverse illnesses completely or end medical problems permanently. Many diseases that cannot be cured are still treatable.

Types of therapies

By therapy composition

Treatments can be classified according to the method of treatment:

by matter

- by drug: pharmacotherapy, chemotherapy, mesotherapy
- by medical device
- by gene: gene therapy
- by gold: chrysotherapy (aurotherapy)
- by hormone: hormone therapy
- by organism: biotherapy
    - by virus: virotherapy
    - by bacteriophage: phage therapy
    - by maggot: maggot therapy
- by ozone: ozonotherapy
- by salt: speleotherapy
- by serum: serotherapy
- by water: hydrotherapy

by energy

- by electric energy

        - by electricity: electrotherapy
        - by electromagnetic radiation: electromagnetic therapy
        - by magnetic energy: magnet therapy
    - by light: phototherapy
    - by mechanical: manual therapy as massotherapy & therapy by exercise as in physiotherapy
        - by sound: Cymatic therapy, music therapy
    - by radiation: radiotherapy
    - by temperature
        - by heat: thermotherapy
        - by cold: cryotherapy

by human interaction

- by counseling, such as psychotherapy
- by education
- by physical therapy/physical exercise, massage therapy, or acupuncture
- by lifestyle modifications, such as avoiding unhealthy food or maintaining a predictable sleep schedule

by meditation

First or second line

Treatment decisions often follow formal or informal algorithmic guidelines. A *first-line therapy* (sometimes called induction therapy or primary therapy)[2] usually on the basis of clinical evidence for its efficacy in the population at large.[*citation needed*] If a first-line therapy either fails to resolve the issue or produces intolerable side effects, additional agents (*second-line therapies*) may be substituted or added to the treatment regimen.[*citation needed*]

See also

- Classification of Pharmaco-Therapeutic Referrals
- Cure
- Interventionism (medicine)
- Inverse benefit law
- List of therapies
- Mature minor doctrine
- Medicine
- Medication
- Nutraceutical
- Prevention
- Psychotherapy
- Therapeutic inertia
- Therapeutic nihilism, the idea that treatment is useless

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UV-induced skin damage

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Abstract

Solar radiation induces acute and chronic reactions in human and animal skin. Chronic repeated exposures are the primary cause of benign and malignant skin tumors, including malignant melanoma. Among types of solar radiation, ultraviolet B (290–320 nm) radiation is highly mutagenic and carcinogenic in animal experiments compared to ultraviolet A (320–400 nm) radiation. Epidemiological studies suggest that solar UV radiation is responsible for skin tumor development via gene mutations and immunosuppression, and possibly for photoaging. In this review, recent understanding of DNA damage caused by direct UV radiation and by indirect stress via reactive oxygen species (ROS) and DNA repair mechanisms, particularly nucleotide excision repair of human cells, are discussed. In addition, mutations induced by solar UV radiation in *p53*, *ras* and *patched* genes of non-melanoma skin cancer cells, and the role of ROS as both a promoter in UV-carcinogenesis and an inducer of UV-apoptosis, are described based primarily on the findings reported during the last decade. Furthermore, the effect of UV on immunological reaction in the skin is discussed. Finally, possible prevention of UV-induced skin cancer by feeding or topical use of antioxidants, such as polyphenols, vitamin C, and vitamin E, is discussed.

Keywords: Ultraviolet light (UV); DNA damage; DNA repair; Reactive oxygen species (ROS); Nucleotide excision repair (NER); Transcription-coupled repair (TCR); UV-apoptosis; Protein kinase C (PKC); Immunosuppression; Olive oil; Prevention; Mutation

1. Introduction

Chronic repeated exposures to sunlight from childhood are epidemiologically shown to be the main cause of skin cancers. Ultraviolet B radiation (UVB), a minor component of sunlight reaching to the earth surface, is experimentally demonstrated to be the most effective light to induce skin cancer in animals, and can cause DNA damage, particularly cyclobutane pyrimidine dimers (CPDs) and (6–4) photoproducts which induce mutation in the epidermal cells, leading to the development of cancer cells.

UVB is also known to upregulate gene expression through intracellular signal transduction pathways, which may contribute to developing skin cancer at the tumor promotion stage. In addition, UVB is proved to suppress immune reaction, and to induce tolerance to antigens,

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which had been applied topically or systemically in experimental animals. These three effects of UVB on the skin are understood to cooperatively contribute to producing skin cancer in humans.

Ultraviolet light A (UVA) and UVB radiation are proved to produce DNA damage directly and indirectly through oxidative stress. Further, reactive oxygen species (ROS) are shown to activate transcription factors, such as AP-1 and NFkB, which may contribute to cell proliferation and/or apoptotic cell death. In this review, roles of ROS for UV-induced skin cancer development and possible preventive effects of antioxidants on UV-carcinogenesis are discussed.

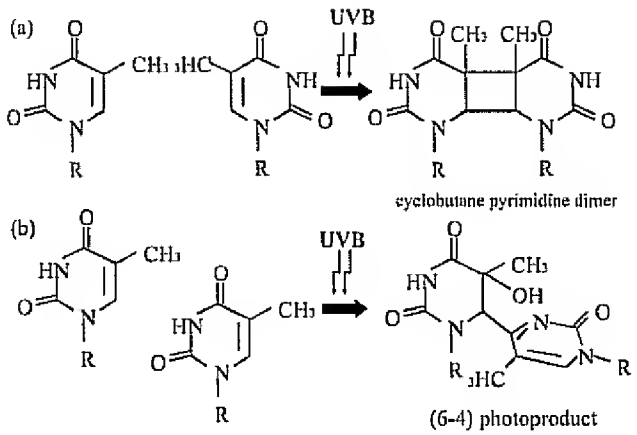

Fig. 1. Adjacent pyrimidine bases on the same stand pyrimidine dimer (Fig. 1a) or (6–4) pyrimidine–pyrrimidone photo product (Fig. 1b) alter absorbing UVB light energy.

2. DNA damage caused by UV radiation and ROS

The most cytotoxic and mutagenic waveband among types of solar radiation corresponds to UVB light. DNA bases directly absorb incident photons within this narrow wavelength range. The phototoxic effect of UVA radiation is much lower than UVB radiation. DNA is not a chromophore for UVA radiation (Rosenstein and Mitchell, 1987), but could be damaged by photosensitization reaction initiated through absorption of UVA by unidentified chromophore.

2.1. Effect of UVB light on DNA

A number of studies using UVC radiation (254 nm) have been conducted to demonstrate the effect of UV on DNA (Mitchell et al., 1991), since UVC is close to the maximum absorption spectrum of DNA to initiate photochemical reactions and is also available as nearly monochromatic light source. The effects of UVB radiation on DNA are mostly caused by the formation of dimeric photoproducts between adjacent pyrimidine bases on the same strand (Fig. 1). The major class of lesions produced is *cis–syn* CPDs. Pyrimidine–pyrimidone (6–4) photoproducts [(6–4) pp] are the second most prevalent adducts formed in DNA by UVB radiation (Mitchell, 1988; Clingen et al., 1995). The yield of (6–4) pp is 5–10-fold less than that of CPDs (Eveno et al., 1995). (6–4) pp are converted to Dewar isomers by UVB rediation. (6–4) Adducts exhibiting a cytosine at their 5′-end may undergo deamination. The number of CPDs formed in a basal cell of human epidermis after exposure to three minimal doses of solar light about 60 min exposure at noon in the summer in Kobe, Japan (34°N) is calculated to be approximately 100 000 per cell (Ichihashi et al., 1998).

Among CPDs, thymine–cytosine (TC) and cytosine–cytosine (CC) dimers are shown to be the most mutagenic, since TC→TT and CC→TT mutations are frequently found in the p53 gene of UV-induced cancer cells (Daya-Grosjean et al., 1995). In the case of TT dimers, the major UV-induced photoproducts in humans are poorly mutagenic, since DNA polymerase preferentially incorporates 'A' residue opposite to non-instructional lesions, restoring the original seguence (A–T). (6–4) pp may be less mutagenic, since it is repaired efficiently compared to CPDs. Actually, 90% (6–4) pp are shown to be repaired at 3 h after irradiation (Nakagawa et al., 1998). In addition to pyrimidine photoproducts, and adenine residue, which can either dimerize with an adjacent adenine or add to an adjacent thymine upon exposure to UVB radiation. The quantum yields of these photoproducts are very low, but these may contribute to the biological effects of UV light, since adenine–thymine adduct is shown to be mutagenic (Zhao and Taylor, 1996).

2.2. DNA damage caused by ROS

Purine photoadduets have recently attracted the attention of photobiologists because the oxidation of guanine oceurs upon exposure of isolated DNA to UVC and UVB light, in the absence of a photosensitizer. This may be accounted for by the formation of singlet oxygen from the triplet state of purine and pyrimidine bases, only a contribution of an electron transfer at the nucleoside level (Ito and Kawanishi, 1997). Electron transfer or singlet molecular oxygen produced by UVB and UVA radiation targets DNA base guanine, giving rise to 8-hydroxydeoxyguanosine (8-OHdG) in the strand DNA (Cadet et al., 2000). 8-OHdG (Fig. 2) is shown to be a ubiquitous maker of oxidative stress (Kasai and Nishimura, 1984) sinee it can be generated under various agents including peroxynitrite,·OH radieal, one-electron oxidation oxidants and singlet oxygen.

8-OHdG is a miscoding lesion causing G to T transversion although it represents only a minor fraction of UV-induced mutation, even in the UVA region (Cheng et al., 1992). UV radiation also induces a much wider range of DNA damage, such as protein-DNA crosslinks, single strand breaks, and thymine glycol.

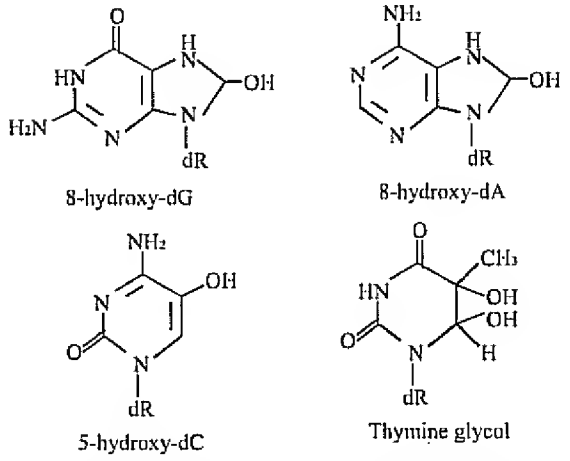

Fig. 2. The major DNA lesions produced by oxidative damage, 8-oxoguanine, thymine glycol, pyrimidine hydrates and urea.

3. DNA repair mechanisms in human skin

Important mechanisms in human cells to avoid the potential mutation in UV-induced-damaged sites are to completely repair the damage by nucleotide exeision repair (NER) before replication, or synthesize DNA using postreplication repair speeifie DNA polymerase which is free from error. NER is a highly conserved strategy for repairing a variety of bulky DNA damages, such as CPDs and (6–4) pp (Mitehell et al., 1985; Wood, 1997). Base change, sueh as 8-OHdG, is repaired by base excision repair (BER) system (Wood, 1996; Krokan et al., 1997) using glycosylase in combination with replication protein A (RPA), proliferating cell nuclear antigen (PCNA) and AP endonuelease.

The importanee of NER for prevention of UV-induced skin caneer and benign tumors is well documented by an extremely high occurrence of skin cancer and seborrheic keratoses on sun-exposed areas in xeroderma pigmentosum (XP) patients who have defective NER (Cleaver, 1968; Robbins et al., 1974; Ichihashi et al., 1988; Sijbers et al., 1996). Complementation studies, using new patient's cells with the cells assigned to each of XPs, revealed that at least 7 gene produets of complementation groups (A–G) except XP variant gene product (DNA polymerase η) (Masutani et al., 1999) are involved in NER (Table 1).

NER is a eomplex process involving more than 30 gene products in which the following five steps are identified (Aboussekhra et al., 1995): (1) reeognition of a DNA lesion; (2) single strand incision at both sides flanking the lesion; (3) exeision of a single stranded DNA nucleotide (possibly 24–32 bases); (4) DNA repair synthesis to replace the excised DNA lesion; and (5) ligation of remaining single stranded nick (Fig. 2). Further, it was found that the foeal, not diffusely spread, nuelear localization of unscheduled DNA synthesis takes place during the first and second 3 h repair periods (Nakagawa et al., 1998).

Reeently, the immunomodulatory mediator IL-12 has been shown to enhance NER activity, suggesting a possible role of cytokines in NER (Schwarz et al., 2002). The encoded protein by XPC gene was shown to be tightly associated with

Table 1
Mammalian genes involved in NER

Human gene/protein	Function in NER	Mouse gene	Mouse mutant phenotype
XPC/XPC	Involved in damage recognition. Not required for TCNER. Represented in human XP	Xpc	Defective in NER of the non-transcribed strand of transcriptionally active genes after UV radiation. Skin cancer after UV irradiation. Heterozygous mutants also prone to skin cancer. Liver and lung tumours after exposure to chemicals (AAF)
RAD23B(HHR23B)/HRAD23B	Binds to XPC. Involved in damage recognition. No human mutants known	Rad23B	No NER-defective phenotype observed. Mice viable but small
XPA/XPA	Involved in damage recognition. Represented in human XP	Xpa	NER defective. Skin cancer after UV radiation or exposure to chemicals (benz[a]pyrene and DMBA)
RPA1/RFA1	Subunit of trimeric RFA complex. Involved in damage recognition. No human mutants known	Rfa1	Not available
XPB/XPB	Subnit of core TFIIH complex. 3'→5'DNA helicase. Promotes bubble formation. Represented in human XP/CS syndrome	Xpb	Embryonic lethality
XPD/XPD	Subnit of core TFIIH. 5'→3' DNA helicase. Promotes bubble formation. Represented in human XP, XP/CS syndrome and TTD.	Xpd	Embryonic lethality. An allele that mimics a mutation in human TTD is viable. These mice are NER defective and have TTD. They also manifest skin cancer after UV irradiation
XPG/XPG	3' DNA-structure-specific endonuclease. Required for bimodal incision. Represented in human XP and XP/CS syndrome.	Xpg	NER defective. Mice viable but runted, indicating a vital function
ERCC1/ERCC1	5' DNA-structure-specific endonuclease with XPF. Required for bimodal incision. No human mutants known	Ercc1	NER defective. Mice runted or nonviable, indicating a vital function
XPF/XPF	5' DNA-structure-specific endonuclease with ERCC1. Required for bimodal incision. Represented in human XP	Xpf	Not available
DDB1/DDB1	Forms a complex with DDB2. Complex defective in individuals with XP-E	Ddb1	Not available
DDB2/DDB2	Forms a complex with DDB1. Complex defective in individuals with XP-E	Ddb2	Not available
CSA/CSA	Required for TCNER. Represented in human CS	Csa	TCNER defective. No obvious CS phenotype. Skin cancer after UV irradiation
CSB/CSB	Required for TCNER. Represented in human CS	Csb	TCNER defective. No obvious CS phenotype. Skin cancer after UV irradiation

one of the two human homologues of the yeast RAD23B (hHR23B) (Sugasawa et al., 1998). It is very likely that the XPC–HR23B complex is essential to recognize DNA lesions in the genome, and XPA–RPA complex participates in a later recognition step of the NER process. Binding of XPC–hHR23B to a DNA lesion induces local unwinding, enabling other repair proteins access to the damaged site. In the next step, recruited TF II H binds to XPC–hHR23B complex as shown in Fig. 1. XPB and XPD proteins have 3′–5′ and 5′–3′ helicase activity. The damage site is incised by XPG and XPF-ERCC-1 complex proteins at 3′- and 5′-incisions sites, respectively, although whether the 5′- and 3′-incision can be made independently from each other, remains to be solved. DNA polymerase δ or ε is involved in NER, and PCNA is required for DNA synthesis

by DNA polymerase δ and ε. Finally, DNA ligase 1 might be carrying out the ligation of the repair patch (de Boer and Hoeijimakers, 2000). XPE gene product is suggested to be involved in NER by binding to the DNA damaged site, so it is recognized as a damaged DNA binding protein (DDB). There are two proteins involved in the binding activity, p125 (DDB1) and p48 (DDB2) (Nichols et al., 1996; Reardon et al., 1993). Hwang et al. (1998) suggested that the p48 protein is essential for CPDs, which was been shown to mutat in XPE cells. DDB heterodimers are not involved in the repair of (6–4) pp of global genome.

There are two other hereditary human diseases associated with a defect in NER: Cockayne's syndrome (CS) and a photosensitivity form of trichothiodystrophy (TTD). Some patients show the combined features of XP and CS. The striking difference between these two diseases is that XP patients develop UV-induced skin cancer, whereas CS and TTD patients do not, despite their photosensitivity. CS (Cleaver and Kraemer, 1995) is a rare photosensitive disorder with defective NER having a wide variety of clinical symptoms including dwarfism and neurological abnormalities, but not associated with an enhanced incidence of skin cancer. At the cellular level, CS cells are hypersensitive to the cytotoxic and mutagenic effects of UV and are characterized by delayed recovery of DNA and RNA synthesis after UV exposure (Mayne and Lehmann, 1982). It is extremely rare, but mutations in *XPB*, *XPD* or *XPG* genes can lead to a combined XP–CS phenotype. TTD patients, also called PIBIDS, show photosensitivity, ichthyosis, sulfur-deficient brittle hair and nails, intellectual impairment, decreased fertility, and short stature. PIBIDS patients have mutations in XPB or XPD gene, components of TF II H, suggesting that these genes are involved in both DNA repair and DNA transcription. It is reasonable to assume that mutations that only affect DNA repair function of XPD could lead to XP, whereas in XP–CS and TTD (at least) the transcription function is modified, and therefore, also the transcription-coupled repair (TCR) pathway (van Steeg and Kraemer, 1999). Eveno et al. (1995) have found that several cell lines from PIBIDS display wild-type or nearly wild-type (50–70%) repair of (6–4) pp in global genome repair (GGR), suggesting a role of (6–4) pp repair in preventing skin cancer formation in TTD. As already mentioned, two NER pathways are known to exist, GGR and TCR (Bohr et al., 1985) (Fig. 3).

3.1. Transcription-coupled repair

Recently, links between DNA damage, repair and transcription began to be disclosed in prokaryotic and eukaryotic cells. Bohr et al. (1985) found that UV-induced CPDs in actively transcribing genes is preferentially repaired compared to non-transcribing parts of the genome in hamster and human cells. Subsequently, it was shown that rapid repair was targeted to the transcribed strand of an active gene (Vreeswijk et al., 1994). The precise mechanisms underlying TCR is not clear yet, but CSA and CSB gene products are essential for TCR. Another factor required for TCR is RNA polymerase II installed at a DNA damaged sites. CS cells show a specific defect in the rapid repair of CPDs in the transcribed strand of active genes. TF II H has dual function in NER and initiation of transcription.

3.2. Global genome repair

GGR acts on DNA lesions throughout the genome. XPC protein is essential for the damage recognition and repair of both CPDs and (6–4) photoproducts by GGR (Sancar, 1994). The damage recognition is a rate-limiting step in the process, and depends on the extent of distortion of DNA helical structure by a lesion. (6–4) pp is repaired much faster than CPDs, possibly due to severe distortion of the DNA helix. Further, it has been recently shown that heterodimer DDB is essential for GGR for initial recognition of CPDs, but not for (6–4) pp.

3.3. Base excision-repair for ROS-induced DNA damage

Endogenously formed DNA damage produced by ROS, hydrolysis, and methylating agents is

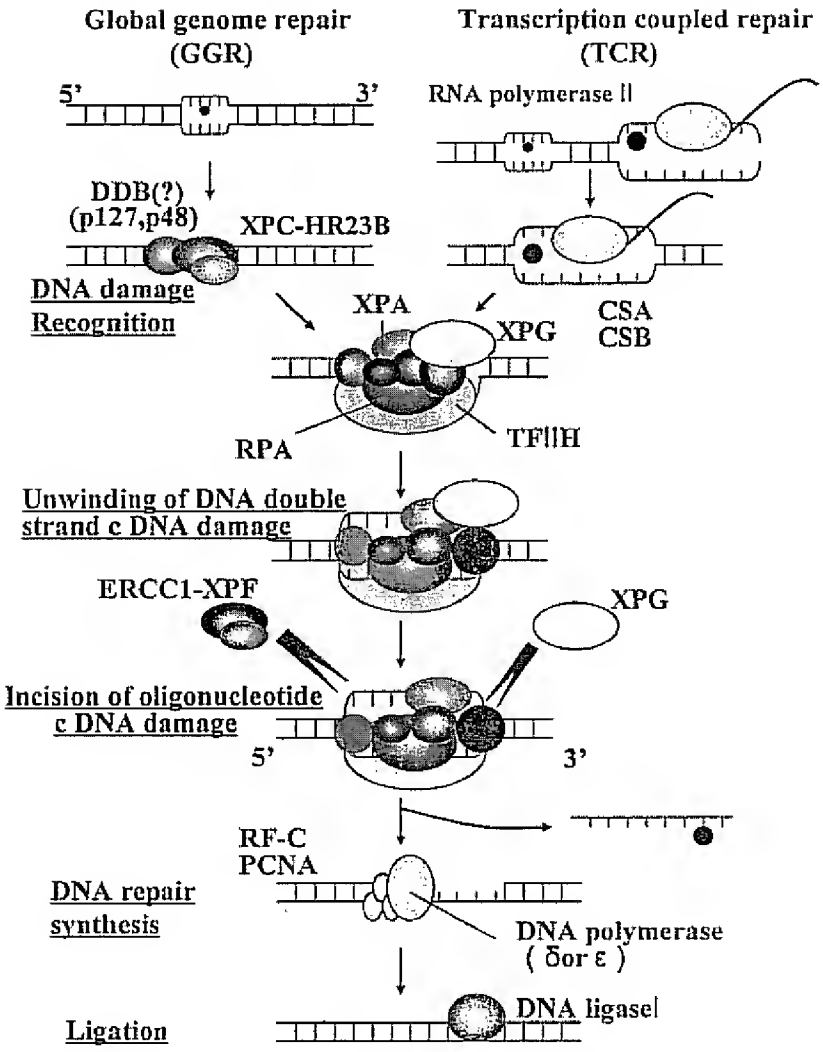

Fig. 3. NER pathways in mammalian cells. GGR and TCR pathways are known to exist in mammalian cells. XPC protein may play a crucial role in the GGR pathway by binding to hHR23B and then binds together to the DNA damaged site. XPA, TF II H2, RPA and DDB2 are expected to serve as essential common factors in NER pathways.

removed primarily by BER pathway. BER is a multistep process involving the sequential activity of several proteins. Typically, this pathway is initiated by a DNA glycosylase, a protein that recognizes and removes a damaged base, such as 8-oxoguanine (8-oxoG) (Aburatani et al., 1997), uracil, or incorrect base by hydrolyzing the *N*-glycosidic bond. In some cases, DNA glycosylases exhibit not only *N*-glycosylase activity, but also incise at the resulting apurinic/apyrimidinic (AP) site, cleaving 3′ to the abasic residue. In *Escherichia coli*, three enzymes, Mut M, Mut Y and Mut T, are known to repair errors in DNA caused by 8-oxoG. Mut M protein excises 8-oxoG paired with cytosine in DNA and initiates BER, and MutY protein excises adenine paired with 8-oxo-G (Krokan et al., 1997; Wilson and Thompson, 1997). Human cells also have similar repair equipment, OGG1 gene (Nishimura, 2002), encoding an 8-oxoG DNA glycosylase (a functional human homolog of Mut M protein). There are 7 spliced forms of OGG1. Among these, hOGG1-1a (36

kDa) is located in the nucleus, while a 40-kDa polypeptide corresponding to a processed form of OGG1-2a is located on the inner membrane of the mitochondria. It has been shown by using purified human proteins that efficient and complete repair of 8-oxoG lesions requires only hOGG1, the AP endonuclease HAP1, DNA polymerase (Pol) beta and DNA ligase 1. Addition of PCNA had a slight stimulatory effect on repair. Further, in the presence of DNA ligase I (Pascucci et al., 2002), the repair was confined to 1 nt replacement. Cellular hOGG1-1a-mediated BER activity is inhibited by exposure to NO which nitrosylates hOGG-1 through zinc ejection (Suzuki et al., 1998). NO generated after UV exposure not only causes DNA damage, but also prevents DNA repair, leading to higher mutation and risk of carcinogenesis. Further, recent studies indicate that two major oxidative DNA damages, 8-oxoG and thymine glycol are excised from DNA in vitro by the same enzyme system responsible for removing pyrimidine dimers and other bulky DNA adducts. Neurodegeneration of XP patients could be caused by defective repair of DNA lesions that are caused in neuronal cells by ROS (Reardon et al., 1997).

4. Mutations induced by UVB in NMSC cells

The general understanding of carcinogenic mechanisms is the hypothesis of clonal expansion of a cell having mutations of oncogenes and tumor suppressor genes (Rees, 1994). Oncogenes and tumor suppressor genes are suggested to have crucial roles on the control of the cell cycle, maintenance of gene integrity, cell proliferation and differentiation. These genes are also categorized into two groups, gatekeeper genes which usually control cellular proliferation and regulate apoptosis, such as *Rb*, *APC and p53*, and caretaker genes which maintain the integrity of the genomes, such as *XP*, *MMR*, *CS*, *ATM*, *BRCA-1*, and *BRCA-2* (Levitt and Hickson, 2002).

CPDs and (6–4) pp produced by solar UVB radiation are mostly repaired effectively without mistake, but incorrect repair of these lesions rarely induces mutations of oncogenes, such as *ras* and tumor suppressor genes, such *as p53* or *PTCH*. These mutations render cells to transform and to immortalize, leading to malignant tumor cells. The real mutations in these genes are demonstrated in basal and squamous cell carcinoma cells in humans (Rees, 1994; Levitt and Hickson, 2002; Campbell et al., 1993). CPDs and (6–4) pp are the major mutagenic photoproducts, which give rise to mutations characterized by C to T and CC to TT transitions located at sites of pyrimidine–pyrimidine sequences (Miller, 1985; Ziegler et al., 1993). The CC to TT tandem mutation is an absolutely specific marker of UV-induced gene alteration. These mutations are recognized to be a signature of sun exposure (Brash et al., 1991).

C to T transition and CC to TT tandem mutation are found in *p53* and *PTCH* tumor suppressor genes (Gailani et al., 1996) and *ras* oncogene (Nishigori et al., 1994; Brash et al., 1996) isolated from skin cancer developed on sun-exposed areas. Mutation of *p53* in human subjects is very frequently found, more than 90% of squamous cell carcinoma (SCCs) and around 50% of BCCs suggesting an essential role of wild-type *p53* gene product for keeping cells in normal conditions (Brash et al., 1996). Similar results have been obtained in skin tumors that have been isolated from XP patients.

p53 mutation site of non-XP subjects is equally divided over both transcribed and non-transcribed strands, whereas *p53* mutation site of skin tumor from XP patients mostly distributed on the non-transcribed strands (Kraemer, 1997). In a study on *PTCH* gene mutation of XP subjects with mostly XPC, 63% of the mutation was CC to TT tandem mutations, compared to 11% in non-XP BCC (Kraemer, 1997). These results of XP patients may be due to study bias analyzing mostly XPC subjects who have GGR defect of NER.

Mutations on *p53* seem to be an early event in UV-induced skin carcinogenesis, since *p53* mutation is found in nearly 50% of actinic keratosis (AK) (Taguchi et al., 1994; Ziegler et al., 1994), premalignant stage of SCC. By immunohistochemical analysis, we showed that approximately 50% of cases of AK and SCC were positive for p53 protein (Nagano, et al., 1993), although protein staining of p53 by antibodies does not always indicate a point mutation in *p53* gene. Ziegler et al.

(1994) showed that 24 out of 45 AK tissue samples had a total of 35 mutations. Further, they found that 89% the mutations occurred adjacent to pyrimidines and most were C to T or CC to TT alterations characteristic of UV mutations. Further, it has been found that *p53* mutations are higher in normal skin on sun-exposed areas without any pathological abnormalities compared to those on covered areas, by analyzing mutations at codon 247/248 of the *p53* gene using an allele-specific polymerase chain reaction (Ouhtit et al., 1997). In addition, the mutation frequency in the age group over 60 years was higher than that in the younger group. Since mutated *p53* is not able to induce apoptotic cell death which eliminates heavily damaged cells having higher possibility of mutations in any other genes, Brash et al. (1996) proposed that *p53* mutated cells on sun-exposed skin must exhibit clonal expansion, due to accumulation of changes in other genes.

Patched gene (*PTCH*) was first identified to mutate in BCC of nevoid basal cell carcinoma syndrome (Hahn et al., 1996; Johnson et al., 1996) and later in sporadic BCC (Aszterbaum et al., 1998). Initially, *PTCH* was isolated in drosophila as a segment polarity gene involved in the development and differentiation. The *PTCH* gene encodes a transmembrane protein (12 membrane spanning domain with two extra-cellular loops) similar to the ABC transporter family. The sonic hedgehog protein, a ligand of PTCH protein, binds to PTCH receptor and deprives the inhibitory function of PTCH protein on the smoothened (SMO) protein, having seven span transmembrane protein, leading to TGF-β and WNT family activations (Fig. 4). *PTCH* has been shown to mutant in around 50–60% of sporadic BCC (Rady et al., 1992). We found a high level of *PTCH* mutation by competitive reverse transcription-polymerase chain reaction in BCC, but not in other skin tumors except in a Bowen's disease, indicating that the *PTCH* gene plays a crucial role in BCC genesis (Nagano et al., 1999). Furthermore, overexpression of SHH was shown to induce BCC in mice (Dahmane et al., 1997), and mutation of *SMO* gene was also identified in sporadic BCC (Xie et al., 1998). These findings indicate an important role of SMO as a signaling molecule of the SHH-receptor complex and provide direct evidence that mutated *SMO* gene can function as an oncogene in BCCs. Xie et al. (2001) recently found that Gli1 can activate platelet-derived growth factor receptor α (PDGFR α) in C3H10T1/2 cells. Functional upregulation of PDGFR α by Gli1 is accompanied by activation of the ras-ERK pathway associated with cell proliferation. A high level of expression of PGGFR α in BCCs of mice and humans are relevant to a role of Gli1, the downstream molecule of the SHH pathway. They suggested that increased expression of PDGFR α might play a role in BCC genesis through altered hedgehog pathway. Typical UV-induced mutations of the *PTCH* are found prominently in XP's BCC and in particular, a significantly higher level of (63%) of the UV signature tandem mutations (CC→TT) is found compared to sporadic BCC (11%) in healthy subjects (Daya-Grosjean and Sarasin, 2000).

5. ROS as promoter in UV-carcinogenesis and as inducer of UV-apoptosis

5.1. Activation of MAP kinase

Ultraviolet radiation is a potent inducer of superoxide radical ($^{\bullet}O_2^-$), hydrogen peroxide (H_2O_2) and hydroxy radical ($^{\bullet}OH$), which have been implicated in cutaneous aging including benign and malignant tumors, and various inflammatory disorders (Cerutti, 1985). UVB may produce $^{\bullet}O_2^-$, and UVA may produce $^1O_2$ possibly through chromophores, such as porphyrin in skin. Devary et al. (1992) showed that by UVC radiation, tyrosine kinases of the Src family increase, followed by activation of Ha-ras and increased phosphorylation of Raf-1, then activate c-Jun and other AP-1 proteins. In this signaling cascade, ROS is suggested to play a crucial role, since the antioxidant, *N*-acetylcystein (NAC), suppressed UVC-induced activation of mitogen-activated protein kinases (MAPK) leading to AP-1 and NFkB activation. Further, transcription of many early genes is mediated by the sequential activation of cytoplasmic protein kinases and MAPK plays a

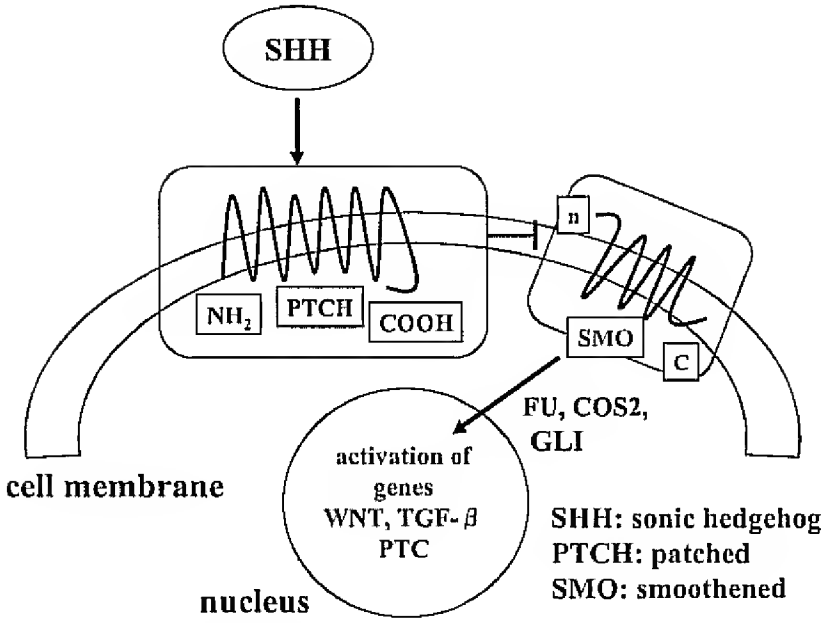

Fig. 4. Proteins in sonic hedgehog signaling pathway are involved in BBC tumor genesis. The binding of SHH to its receptor patched (PTCH), a 12-span transmembrane products of patched gene, releases the suppressive effect on smoothened (SMO protein). If PTCH or SMO is mutationally activated, SMO gets released from the membrane, more into the nucleus and activates transcription factor Gl-1 upregulating the expression of WNT, TGF β and PTCH.

major role in initiating and coordinating these gene responses.

Three distinct MAPK signal transduction pathways, the extracellular signal regulated kinases 1 and 2 (ERK1/2), c-Jun *N*-terminal kinase (JNK) and p38 MAPK, the mamalian homolog by yeast HOG1, also known as CSBP have been identified (Xia et al., 1995; Su and Karin, 1996). ERKs are primarily activated in response to growth factors and phobor esters, and JNK participates in growth factor signaling as well as responding to various stress events such as UVR and inflammatory cytokines. p38 is known to be a stress-induced signaling pathway. ERK 1/2 and p38 signaling pathways are shown to be activated by UVB via ROS in cultured keratinocytes, although it is not clarified yet whether apoptosis signal-regulating kinase 1, one of the activators of ERK is involved in UV-stress response (Ichijo, 1999). The time-dependent activation of ERK1/2 and p38 are distinct, and UVB-induced ERK1/2 activation is downregulated more rapidly than p38. Ascorbic acid strongly blocks ERK1/2 and p38 activation by UVB and hydrogen peroxide (Peus et al., 1999). Cell death by UVB radiation is rescued by ERK1/2 activation, whereas inhibition for ERK1/2 increases UV-induced cell death.

H_2O_2 is produced in the cells following UVB irradiation and stimulates phosphorylation of EGFR, suggesting an important role of H_2O_2 in cellular signaling (Owen et al., 2000). H_2O_2 produced by UVB irradiation is considered to mediate ERK1/2 activation, since antioxidants shown to inhibit UVB-induced H_2O_2 formation suppresses ERK1/2 activation. H_2O_2 formed by UVB may mediate ERK1/2 activation through upstream substances such as ras, raf and MEK 1 and 2 after EGFR phosphorylation (Peus et al., 1998). A substance, which inhibits UV-induced ERK1/2 activation and activates JNK after UV radiation, may play some role in preventing UV-carcinogenesis, possibly by enhancing apoptotic cell death.

The effect on AP-1 transcription activity results, in part, from enhanced phosphorylation of the c-Jun NH_2-terminal activation domain. JNK1, a distant relative of the MAP kinase group is activated by dual phosphorylation at Thr and

Tyr during UV response. JNK1 binds to the c-Jun transcription domain and phosphorylates it on Ser-63 and Ser-73. This process is thought to be responsible for UV-induced tumor promotion (Derijard et al., 1994).

5.2. A role of PKC δ in UV-induced apoptosis

Multiple signaling pathways appear to be involved in the apoptosis of keratinocytes following UV exposure, including production of tumor necrosis factor-α (TNF-α), activation of CD95 (FAS/APO-1) (Aragane et al., 1998; Schwarz et al., 1995; Rehemtulla et al., 1997), and activation of MAPK, JNK. PKC is a serine/threonine–protein kinase family consisting of more than 10 isoforms (Nishizuka, 1995), that is involved in a variety of signal transduction pathways. The PKC isoforms have the regulatory and catalytic domains in the amino- and carboxyl-terminal halves, respectively. PKC can be classified into three groups, cPKC, nPKC and aPKC, based upon structural differences in their regulatory domains, which require specific co-factor in each group.

PKC δ is one of the nPKC isoforms expressed ubiquitously among the cells and tissues including keratinocytes (Gherzi et al., 1992; Gschwendt, 1999). Overexpression of the PKC isoform causes growth inhibition and differentiation in cultured cells (Watanabe et al., 1992; Ohba et al., 1998). In addition, a proteolytic fragment of PKC δ containing its catalytic domain is produced in cells in response to radiation and DNA damaging agents. The activation of aPKC isoforms is inhibited by UV exposure, and overexpression of an aPKC isoforms can protect against UV-induced apoptosis (Newton, 1995). aPKC isoforms have also been implicated in the activation of AP-1 by UV light (Denning et al., 1995). PKC δ is only expressed in differentiating keratinocytes (Koizumi et al., 1993). Activation or increased expression of PKC α and PKC δ is linked to the differentiation (Koizumi et al., 1993; Ueda et al., 1996; Lee et al., 1997). In addition, cPKC and nPKC isoforms are the molecular target for tumor promoting phorbol esters in skin chemical carcinogenesis (Nishizuka, 1995, 1984). PKC δ is activated by UVB radiation in normal human keratinocytes, and inhibition of PKC δ significantly suppressed UV-induced apoptosis. Further, inhibition of caspases blocked the UV-induced cleavage of PKC δ and apoptosis, suggesting a pivotal role of PKC δ activation as the UV-induced death effector in normal human keratinocytes (Rehemtulla et al., 1997).

Recently, three tyrosine residues of PKC δ can be phosphorylated by H_2O_2 at Tyr-311 and Tyr-332 located in the hinge region between three regular and catalytic domains and Try-512 in the activation loop of the catalytic domain (Konishi et al., 2001). The phosphorylation at Tyr-311 site by Lck, a non-receptor type tyrosine–protein kinase, enhanced its basal enzymatic activity in the absence of 1,2-diacylglycerol. Therefore, it seems that H_2O_2 treatment induces tyrosine phosphorylation of PKC δ and that the modification reaction has a critical role for the generation of the catalytically active form of the PKC isoform without proteolysis, that may contribute to apoptotic cell death (Konishi et al., 2001).

It has been shown that UVC irradiation induces phosphorylation and activation of PKC δ in cultured HaCaT cells, although catalytic fragment of PKC δ is not generated. Further, UV-induced apoptosis was prevented by NAC, a potent radical scavenger, and inhibited tyrosine phosphorylation of PKC δ induced by UV-radiation (Fukunaga et al., 2001). It is likely that ROS generated in UV-irradiated cells facilitates the tyrosine phosphorylation reaction of PKC δ, leading to promotion of cell death.

Several non-receptor type tyrosine–protein kinases such as Src, ZAP-70 (Fukunaga et al., 2001), Pyk2 (Tokiwa et al., 1996) Syk (Qin et al., 1997) and Btk (Kawakami et al., 1998), and receptor type tyrosine–protein kinases, such as epidermal growth factor receptor (Sachsenmaier et al., 1994; Coffer et al., 1995), insulin receptor (Warmuth et al., 1994), and c-Ret (Kato et al., 2000) are also activated by UV irradiation. Among these, it is required to determine which tyrosine–protein kinases phospholylates PKC δ in UV-irradiated cells. In addition to PKC δ, JNK, as described already, has also been demonstrated to participate in apoptosis process. It is plausible that PKC δ promotes UV-induced apoptosis in cooperation

with other protein kinases and cell death signal pathways.

6. UV induces immunosuppression which may play a crucial role in skin cancer development

6.1. Local and systemic immunosuppression

UVB at high doses and even such a low level as one minimal erythema dose (MED) can impair host immune surveillance for skin cancers in rodents possibly by modulating the expression of co-stimulatory function of epidermal Langerhans cells (LCs) and lymphocytes. Initially, Fisher and Kripke (1997) described that skin tumors developed in adult mice exposed to high dose of UVB radiation for prolonged periods of time were rejected when transplanted to syngenic healthy mice, but continued to grow when transplanted to mouse skin pre-exposed to UVB radiation before tumor cell transplantation. Further, mice chronically exposed to UVB radiation displayed a systemic defect in antigen presentation (Fig. 5). The ability of these mice to respond to alloantigens and to various other antigens was impaired.

In early 1980s, low doses of UVB radiation delivered to the skin deprived the ability to respond to hapten painted on irradiated skin sites, although haptens painted on untreated skin sites induced contact hypersensitivity (Elmets et al., 1983). Further, it was demonstrated that the unresponsiveness could be transferred with viable lymphocytes to naïve recipients, indicating that suppressor T cells may be responsible (Fisher and Kripke, 1982). The mechanisms of this local immunosuppression are complex and proposed to involve a number of components: (1) a direct effect on the antigen presenting activity of LCs and other antigen presenting cells in the skin (Simon et al., 1991; Kripke, 1984); (2) local production of immunomodulatory cytokines, TNF-α (Vermeer and Streilein, 1990); (3) the infiltration of macrophages into the skin which have different antigen presenting capabilities from the normal resident APC (Cooper et al., 1993); and (4) in the case of suppression of the DTH response to herpes virus injected locally into UV-irradiated

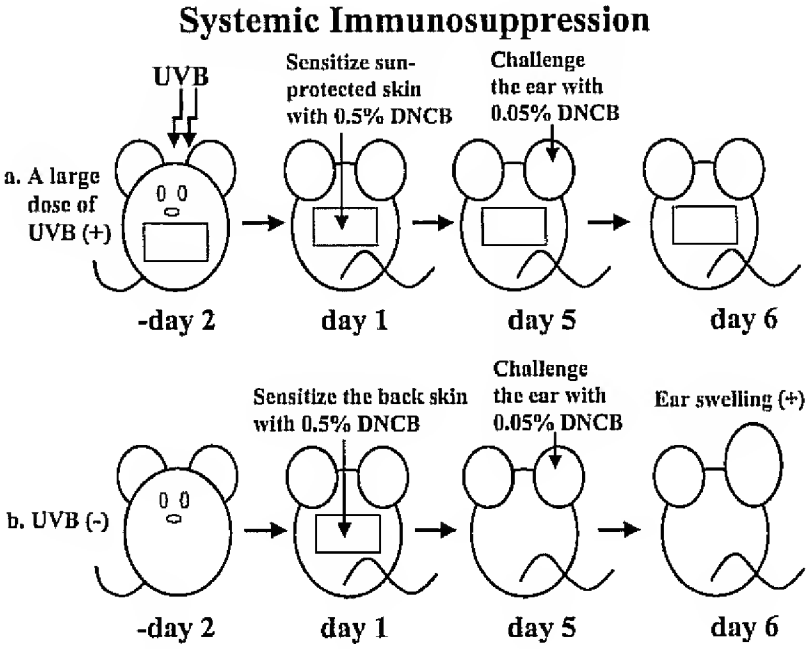

Fig. 5. Systemic immunosuppression by high dose of UVB irradiation in mice. When hapten DNCB was painted on the intact skin of the mouse, which had received a large dose of UVB in an another area 4 days before sensitization, the mouse ear challenged with DNCB did not show any response, suggesting systemic immunosuppression by a large dose of UVB irradiation.

skin site (Howie et al., 1998), the isomerization of urocanic acid to its immunosuppression *cis*-isomer is suggested to be responsible (Norval et al., 1990). In systemic immunosuppression, it is suggested that DTH could be modulated by IL-10, possibly released from UV-irradiated KC, and CHS might be modulated by TNF-α, since antibody against IL-10 and TNF-α suppresses DTH and CHS, respectively, (Rivas and Ullrich, 1992, 1994).

IL-12 is known to induce TH1-specific immune responses and to inhibit the development of TH2 cells (Trinchieri, 1998). IL-12 is also shown to overcome UVB-induced systemic immunosuppression of CHS and DTH reactions (Schmitt et al., 1995). The mechanisms of IL-12 to recover or prevent UVB-induced systemic immunosuppression are not clear yet. We have previously reported that IL-12 enhances the accessory cell function of LCs in a mixed epidermal cell–lymphocyte reaction resulting in augmentation of IFN-γ production (Suemoto et al., 1998). To address the question of whether pretreatment of APC with IL-12 could restore the TH1-type response in UVB-induced systemic immunosuppression, we analyzed how IL-12 may restore the suppressed TH1-type response in mice with UVB-induced systemic immunosuppression. For this purpose, furthermore, using an in vitro system, we examined the effects of IL-12 on APC function in UVB-induced systemic immunosuppression. We found that IL-12-pretreated APC could not restore the reduced IFN-γ production.

We further found that anti-CD3 mAB-induced IFN-γ production by T cells from UVB-irradiated mice was not augmented in the presence of anti-CD28 mAb but IL-4 production was enhanced by the addition of anti-CD28 mAb. Further, the reduced IFN-γ production by T cells from UVB-irradiated mice in response to antigen plus APC was restored by adding IL-12 to the culture. Our results indicate that UVB-induced systemic immunosuppression involves impaired Th1-type responses of T cells through CD28 signaling, and that IL-12 recovers the impaired CD28 co-stimulatory signaling in T cells resulting in the restorarion of Th1 responses (Ando et al., 2000).

In early 1990s, it was shown that most skin cancer patients exposed to UVB failed to develop CHS to hapten, whereas about 60% of healthy subjects developed vigorous contact hypersensitivity. These subjects who failed to induce immune reaction were called UV-susceptible, and about 60% of healthy subjects who responded hapten vigorously were called UV-resistant. It was postulated that UV susceptibility might be a risk factor for the development of skin cancer (Yoshikawa et al., 1990). These results demonstrate that UV radiation not only initiates and promotes epidermal normal cell to cancer cell via effects on cellular DNA and intracellular signal transduction, but also interferes with host immunity against the development of skin tumor cells.

6.2. DNA damage may trigger immunosuppression

DNA damage was proposed to initiate UV-induced immunosuppression by the following evidence: (1) UV-induced suppression of CHS in American opossum, whose DNA damage is repaired by visible light-activated photoreactivating enzyme, was completely prevented by exposing opossum skin to visible light immediately after UVB irradiation (Applegate et al., 1989); (2) topical application of T4N5 (bacteriophage T4 endonuclease V, an excision repair enzyme for CPDs in DNA) to UVB-irradiated mouse skin prevented UVB-induced suppression of DTH and CHS responses and induction of suppressor T cells (Kripke et al., 1992); and (3) IL-10 which is shown to be responsible for systemic immune suppression is produced by cultured KC after UV irradiation, but not by KC pretreated with T4N5 suggesting that UV-induced DNA damage may trigger at least in part the production of soluble immunosuppressive mediators, such as IL-10 from KC (Nishigori et al., 1996).

LC densities in chronically sun-exposed skin were remarkably reduced in patients with XPA, but only slightly in normal subjects compared with covered skin. Further, a single irradiation of 3 MEDs induced a large reduction of LCs in 3–7 days in all subjects, but return to preirradiated levels was markedly delayed (28 days) in XPA subjects compared to those (14 days) of normal healthy subjects (Jimbo et al., 1992). The similar marked reduction of LC in XPA gene-knockout

mouse after a small dose of UVB radiation was observed by Miyauchi-Hashimoto et al. (1996). In addition, UV-induced local and systemic immunosuppression to contact hypersensitivity was greatly enhanced in $XPA^{-/-}$ mice. Enhanced suppression of natural killer cells activity of $XPA^{-/-}$ mice exposed to UVB radiation was also demonstrated (Miyauchi-Hashimoto et al., 1999).

6.3. c-UCA may trigger UV-induced immunosuppression

UVB irradiation isomerizes urocanic acid, which may contribute to some of the early immunosuppressive effects of UV, especially in relevance to DTH responses (Norval et al., 1995; Beissert et al., 1997). These events may cause the failure of cutaneous APC to activate Th1 lymphocytes leading to suppressed responses of DTH and CHS, although the exact mechanisms of induction of APC dysfunction and suppresssor T cells are not yet clear.

7. Prevention of UV-induced skin cancer by feeding of and topical use of polyphenols, vitamin C, and vitamin E

7.1. Green tea and black tea

Green tea is one of the most common beverages in the Asia. The principal chemical constituents of green tea are polyphenols, containing (−)-epigallocatechin (EGC), (−)-epicatechin (EC), (−)-epicatechin-3-gallate (ECG) and (−)-epigallocatechin-gallate (EGCG) (Wang et al., 1992; Yang and Wang, 1993). These components are shown to react with cytochrome P450 and inhibit catalytic activities in a dose dependent manner.

Epidemiological studies in Asian countries showed that high green tea consumers (10 cups per day) had the low incidence of prostate and breast cancers compared with those consume less than three cups of green tea per day.

A wide-range of antioxidants has been shown to be effective in preventing against photocarcinogenesis in murine skin. Polyphenols are well known antioxidants. Wang et al. (1994) demonstrated that oral and topical application of polyphenols before UVB irradiation protected mice skin from UV-induced skin cancer development. Further, chronic oral feeding of polyphenols in drinking water was also shown to afford better protection against UV-carcinogenesis than topical use. Wang et al. (1991) also reported inhibitory effects of orally administered black tea, decaffeinate green tea, and decaffeinate black tea on UV-induced benign and malignant tumor formation in SKH-1 mice. In addition, oral administration of caffeine had a strong inhibitory effect on UV-induced skin cancer formation.

The anticancer effects of tea have been attributed to the antioxidant catechins and polyphenols, which may primarily regulate cell cycle progression and induction of p53-dependent apoptosis (Huang et al., 1998). In 2001, Lu et al. (2000) demonstrated that pretreatment of SKH-1 mice with 0.6% green tea (6 mg lyophilized tea solid per ml) administered orally enhanced UV-induced increases in the number of p53-positive cells, p21/WAF-1/CIP-1 positive cells and apoptotic cells in epidermis. These effects may play a role in the inhibitory action of tea in UV-induced carcinogenesis possibly eliminating cells, which may progress into malignant cancer cells.

UV radiation is a potent inducer of ROS, which have been implicated in photoaging and skin cancer development (Beehler et al., 1992). H_2O_2 and UVB radiation have been reported to upregulate expression of genes such as c-fos and c-jun, via phosphorylation of, JNK and p38, leading to the activation of AP-1 and NFkB, which increase cell survival (Raingeaud et al., 1995). The promoting effect of UV radiation-induced ERK activation is inhibited by anti-ROS agents, such as EGCG and ascorbic acid (Peus et al., 1999).

7.2. Phytic acid

Phytic acid, inositol hexaphosphate (IP6), found ubiquitously in plant and animal cells, has been shown to reduce the rate of cellular proliferation both in vivo and in vitro in human colon cancer (Huang et al., 1997). In addition, IP6 has been

shown to inhibit UV-induced signal transduction, particularly blocked UVB-induced AP-1 and NFkB transcriptional activities (Shamsuddin, 1999). IP6 also suppressed UVB-induced phosphorylation of ERK and JNKs, but not p38 kinases (Chen et al., 2001). Taken together, it is suggested that antioxidants, which enhance JNK- and suppress ERK-phosphorylation may increase apoptotic cell death after exposure to UV radiation, preventing skin cells from UV-induced carcinogenesis.

7.3. Olive oil

In the Mediterranean area where olive oil is the dietary fat of choice, the incidence of coronary heart disease and certain cancer is low (Visioli and Galli, 1995). Extra virgin olive oil, which is obtained from whole fruit, is rich in phenolic compound having potent anti-ROS activity. Visioli et al. (1998) showed that hydroxytyrosal and oleuropein are potent scavengers of $^{\bullet}O_2^-$ and inhibitors of neutrophil respiratory burst. Oleuropein has been reported to increase NO production from LPS-challenged mouse neurophils, and also to remove $^{\bullet}O_2^-$, possibly preventing the formation of peroxynitrite.

Recently, we have found that extra virgin olive oil painted the mouse skin immediately after UVB radiation, significantly retarded the onset and reduced the number of skin cancer, but pretreatment with extra virgin olive oil and pre- or post-treatment by regular olive oil neither retarded nor reduced skin cancer formation in UV-irradiated mice. In addition, we showed that ROS-induced DNA damage, 8-OHdG in mice epidermis after a single irradiation of UVB (3.43 kJ/m^2) was apparently reduced by extra virgin olive oil painted immediately after UV irradiation, whereas CPD positive cells, and the grade of positivity were not reduced by post-UV painting of extra virgin olive oil (Budiyanto et al., 2000). In the next step, we further asked which components of olive oil are effective in reducing 8-OHdG production after UVB-treatment. Oleuropein, but not hydroxytyrosol and squalene, reduced 8-OHdG production (Ichihashi et al., 2001). These results suggest that the preventive effect of olive oil on UV-induced skin cancer may be caused at least in part by preventing cellular damage by ROS. We also confirmed enhanced apoptotic cell death of UV-induced HaCaT cells pretreated with oleuropein (unpublished results).

These results strongly suggest that topical use of olive oil after sunbathing in humans may prevent skin cancer formation by reducing ROS-induced DNA damage. In the near future, however, further studies using animal and human skin to get results which provide support for the preventive effect of olive oil on UV-induced skin cancer should be made before concluding that post-use of extra virgin olive oil is recommended to the public.

8. Conclusion

Skin cancers are mostly caused by chronic exposure to solar radiation, which induces activation of oncogenes and inactivation of tumor suppressorgenes. In addition, solar ultraviolet radiation stimulates cell proliferation via signal transduction initiated on cellular membrane. UVB and possibly UVA suppress immune responses, contributing to the development of skin cancer.

In this review, we discussed a role of UV-induced DNA damage in skin carcinogenesis and also recent advances in the understanding of the mechanisms of DNA repair, particularly NER, which play a pivotal role in preventing skin carcinogenesis. Further, we focused on the recent understanding of a role PKC and MAPKs in cell proliferation and apoptosis, initiated by ROS. A role of UV-induced immunosuppression in skin carcinogenesis was also discussed. Our deep understanding of the mechanisms of acute and chronic skin damage caused by solar radiation helps us to find preventive ways for cancer development and photoaging of the skin. Even at present, we can say that everyday use of sunblocks and oral intake or topical use of antioxidants from childhood may effectively prevent photoaging and skin cancer development, which occur at aged.

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